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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
PAK, YONG D	

ART UNIT	PAPER NUMBER
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/664,341	ZDANOVSKY ET AL.	
	Examiner	Art Unit	
	YONG D. PAK	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 September 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-18,21-23,27-46 and 48* is/are pending in the application.

4a) Of the above claim(s) *12-14,21-23,27-29,33,38-40,45 and 46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-11, 15-18, 30-32, 34-37, 41-44, and 48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/30/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed on September, 2009, amending claims 1, 3-4, 9-11, 17, 21-22, 27, 35, 39, and 46, canceling claims 2, 19-20, 25-26, and 47, and adding claim 41, has been entered.

Claims 1, 3-18, 21-23, 27-46, and 48 are pending. Claims 12-14, 21-23, 27-29, 33, 38-40 and 45-46 are withdrawn. Claims 1, 3-11, 15-18, 30-32, 34-37, 41-44, and 48 are under consideration.

Election/Restrictions

Claim 17 is partially directed to non-elected inventions SEQ ID NOs:47, 48, 49, 66, 69-71 and 73-80. For examination purposes, the Examiner will only examine the elected invention, polynucleotide comprising SEQ ID NO:72.

Information Disclosure Statement

The information disclosure statement filed on September 20, 3009 fails to comply with 37 CFR 1.98(a)(3) because it does not include a concise explanation of the relevance, as it is presently understood by the individual designated in 37 CFR 1.56(c) most knowledgeable about the content of the information, of each patent listed that is not in the English language. It has been placed in the application file, but the information referred to therein has not been considered. No translation or concise explanation of JP-2002541767T2 has been filed.

Response to Arguments

Applicant's amendment and arguments filed on September 30, 2009, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Rejections - 35 USC § 112 – 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

In view of the amendment, the rejection of claim 1 and claims 4-11, 17-19, 25, 30-31, 35-37, and 41-44 depending therefrom under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention has been **withdrawn**.

Claims 15-16 and claims 32 and 34 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 15-16 recite the limitation "the heterologous destabilization sequence" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3-11, 15-18, 30-32, 34-37, 41-44, and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Daly, Gilon et al., Bence et al. and Corish et al.

Claims 1, 3-11, 15-18, 30-32, 34-37, 41-44, and 48 are drawn to (A) a fragment of SEQ ID NO:72 which encodes a polypeptide with substantially the same activity as the full-length fusion polypeptide encoded by SEQ ID NO:72 or (B) a polynucleotide

encoding a fusion polypeptide comprising a luciferase and a PEST protein destabilization sequence or a protein destabilization sequence of SEQ ID NO:89 and/or an AU-rich mRNA destabilization sequence and further comprising an inducible promoter and a vector and a mammalian cell comprising said polynucleotide, wherein the half life of expression of luciferase is 20 or 30 minutes or said fusion polypeptide has an enhanced protein degradation relative to a fusion polypeptide comprising only one of the protein destabilizing sequence.

Daly (US Patent No. 7,157,272 – form PTO-892) discloses a polynucleotide encoding a reporter protein, such as a luciferase and GFP, one or more protein destabilizing sequences, such as including a PEST sequence from mODC and a N-terminal degradation signal for ubiquitin system proteolysis, and one or more mRNA destabilizing sequences, such as an AU rich mRNA destabilizing sequence, wherein said destabilizing sequences are C-terminal to the reporter protein, wherein said fusion polypeptide has an enhanced protein degradation relative to a fusion polypeptide comprising only one of the protein destabilizing sequence, and wherein the half-life is about 20-30 minutes (Column 16, lines 18-67, Column 26, lines 36-59, Column 54, line 57 through Column 55, line 20). Daly also discloses vectors comprising inducible/repressible promoters operably linked to the above polynucleotide and optimization of the above polynucleotide optimized for expression in mammalian cells (Column 5, line 65 through Column 6, lines 59 and Column 22, line 7 through Column 23, line 46, and Column 29, lines 25-33).). Daly discloses that the combination of mRNA destabilization and protein destabilization significantly improves the reporter

levels or activity in expression constructs compared to constructs without destabilization elements or with only one type of destabilizing element since protein destabilizing elements reduce the intracellular half-life of a protein and mRNA destabilizing sequences reduce the intracellular half-life of RNA transcript (Column 26, lines 2-24). Daly provides several protein destabilizing sequences, such as ubiquitin, or variant or derivative of ubiquitin or protein degradation signals and several mRNA destabilizing sequence and that multiple combinations can be used (Column 25, lines 39-40, Column 30, lines 13-14, and Column 53, lines 35-38). Daly also discloses that the half life of the reporter protein-PEST is about 2 hours (Column 31, lines 17-27). Daly also discloses that it is advantageous to reduce the half-life of a protein of interest by adding one or more destabilizing elements to confer a level of enhanced degradation on the protein of interest, desirably less than 3, 2, or hour(s), or even less than about 30, 15, 10, 5 or 3 minutes since the half-life of a protein of interest advantageously corresponds to the lowest half-life that provides a steady-state expression level (Column 26, lines 36-49).

The difference between the reference of Daly and the instant invention is that Daly does not teach a polynucleotide encoding a fusion protein comprising the CL1 protein destabilizing sequence of SEQ ID NO:89, which is a C-terminal degradation signal for ubiquitin based proteolysis.

Gilon et al. (form PTO-1449) discloses several protein destabilizing sequence, such as a CL1 sequence (ACKNWFSSLSHFVIHL) which is 100% identical to the CL1 sequence of SEQ ID NO:89, attached C-terminal to the protein of interest and promotes degradation of the protein (See Table 1 on page 2763 of Gilon et al. and on page 31 of

the instant specification). CL1 is a C-terminal signal wich is required for ubiquitination (page 2759). Bence et al. (form PTO-1449) discloses expression of a fusion protein comprising the CL1 sequence and a GFP in a mammalian host cell, wherein the half life of the GFP is 20 to 30 minutes compared to GFP without the CL1 sequence (Pages 1552-1553).

Corish et al. (Protein Eng. 1999 Dec;12(12):1035-40 - form PTO-1449) discloses a polynucleotide encoding a fusion protein comprising a reporter protein and two protein destabilizing sequences, a PEST sequence and a cyclin destruction box (page 1035, right column and Figure 1 on page 1036). Corish et al. discloses that the combination of two protein destabilization sequences produced a reporter protein having decreased half life as compared to the reporter protein having one of the protein destabilizing sequences (abstract), reduction from 5.8 hours to 5.5 hours which equates to 18 minutes. Similar to Daly, Corish et al. provides the benefit of using multiple destabilization sequences to further decrease the half-life of the reporter proteins.

Therefore, in combining the teachings of Daly, Gilon et al., Bence et al., and Corish et al., it would have been obvious to one having ordinary skill in the art to add an additional protein destabilizing sequence of Gilon et al./Bence et al. C-terminus to the reporter protein of the construct of Daly or to substitute the N-terminal degradation for ubiqutin. One of ordinary skill in the art would have been motivated to add the protein destabilizing sequence of Gilon et al./Bence et al. or to substitute the N-terminal degradation signal of Daly with the C-terminal degradation signal of Daly in order to further reduce the half life activity/expression of luciferase or GFP comprised in the

fusion protein of Daly. One of ordinary skill in the art would have had a reasonable expectation of success since Daly and Corish et al. teaches reducing the half-life of a reporter protein such as a luciferase or GFP by using multiple destabilizing sequences, Gilon et al. teaches a C-terminal degradation signal for ubiquitin based proteolysis, and Bence et al. teaches expression of a CL1-GFP fusion protein in a mammalian cell, wherein the half of the GFP is 20 or 30 minutes.

Therefore, the above references render claims 1, 3-11, 15-18, 30-32, 34-37, 41-44, and 48 *prima facie* obvious to one of ordinary skill in the art.

In response to the previous Office Action, applicants have traversed the above rejection. Applicants should note that the rejection has been amended in light of the amendment of the claims.

Applicants argue that the claims are not obvious over Daly and Gilon et al. because applicant is unable to find in the cited portions of Daly and Gilon et al., individually or in combination, an isolated polynucleotide encoding a fusion polypeptide comprising a reporter protein and at least two different protein destabilization sequences both of which are C-terminal to the reporter protein, wherein one heterologous protein destabilization is SEQ ID NO:89 and the second heterologous protein destabilization is a PEST sequence. Examiner respectfully disagrees. In considering the disclosure of a reference, it is proper to take into account not only specific teachings of the reference but also the inferences which one skilled in the art would reasonably be expected to draw therefrom. Daly discloses that multiple combinations can be used, for example PEST at the carboxy-end and a ubiquitin

sequence at the N-end (Column 25, lines 39-40, Column 30, lines 13-14, and Column 53, lines 35-38). Daly discloses that the half life of the reporter protein-PEST is about 2 hours (Column 31, lines 17-27) and Bence et al. (form PTO-1449) discloses expression of a fusion protein comprising the CL1 sequence and a GFP in a mammalian host cell, wherein the half life of the GFP is 20 to 30 minutes compared to GFP without the CL1 sequence (Pages 1552-1553). Therefore, one having ordinary skill in the art would have reasoned from the disclosure of Daly, Gilon et al., and Bence et al. to add the CL1 sequence of Gilon et al./Bence et al. C-terminus to the reporter protein or to use the CL1 sequence of Gilon et al./Bence et al. C-terminus to the reporter protein instead of the ubuquitin sequence at the N-end. The motivation is to further reduce the half life activity/expression of luciferase or GFP comprised in the fusion protein of Daly since Bence et al. discloses expression of a GFP-CL1 wherein the half life of the GFP is 20 to 30 minutes (Pages 1552-1553).

Applicants also argue that the Examiner has failed to provide a rationale for preparing a reporter protein with a shorter half-life than 20-30 minutes. The rejection has been amended. Daly discloses that it is advantageous to reduce the half-life of a protein of interest by adding one or more destabilizing elements to confer a level of enhanced degradation on the protein of interest, desirably less than 3, 2, or hour(s), or even less than about 30, 15, 10, 5 or 3 minutes since the half-life of a protein of interest advantageously corresponds to the lowest half-life that provides a steady-state expression level (Column 26, lines 36-49).

Applicants also argue that applicant is unable to find in the Office Action a reason why one of ordinary skill in the art would have had a reasonable expectation of success in the combination of the cited reference because based on the results of Corish et al. (of record), one skill in the art was apprised that a reporter protein linked to a combination of two different protein destabilization sequences (PEST and a cyclin B1 fragment) did not have a substantially reduced half-life relative to a reporter protein linked to the "dominant" protein destabilization sequence. Examiner respectfully disagrees. Corish et al. discloses a further reduction to 5.5 hours (using two protein destabilization sequences) from 5.8 hours (using one destabilization sequence). A difference of 0.3 hours equates to 18 minutes, which is not marginal since Daly teaches the desirability of reducing the half life as much as possible, to less than 30, 15, 10, 5, or 3 minutes (Column 26, lines 36-49). Therefore, Corish et al. provides further motivation to one having ordinary skill it the art to use multiple destabilization sequences and a reasonable expectation of success in further reducing the half life of a reporter protein using two protein destabilization sequences instead of one. Therefore, one of ordinary skill in the art would have had a reasonable expectation of success since Daly and Corish et al. teaches reducing the half-life of a reporter protein such as a luciferase or GFP by using multiple destabilizing sequences, Gilon et al. teaches a C-terminal degradation signal for ubiquitin based proteolysis, and Bence et al. teaches expression of a CL1-GFP fusion protein in a mammalian cell, wherein the half of the GFP is 20 or 30 minutes.

Applicants also argue that Gilon et al. that the fusion protein comprising the CL1 sequence was expressed in yeast and therefore, one skill in the art wou dnot have a reasonable expectation that CL1 sequence would be useful in a mammalian cell. The rejection has been amended. Bence et al. teaches expression of a CL1-GFP fusion protein in a mammalian cell, wherein the half of the GFP is 20 or 30 minutes.

Applicants also argue that prior to Applicant's disclosure, it was unknown whether different protein destabilization sequences at the C-terminus of a protein of interest could have complementing effect and in view of Corish et al. it was unexpected that different protein destabilization sequences could have complementing effect. Examiner respectfully disagrees. As discussed above, Corish et al. discloses a further reduction to 5.5 hours (using two protein destabilization sequences) from 5.8 hours (using one destabilization sequence). A difference of 0.3 hours equates to 18 minutes, which is not marginal since Daly teaches the desirability of reducing the half life as much as possible, to less than 30, 15, 10, 5, or 3 minutes (Column 26, lines 36-49). Therefore, it would not have been unexpected that that different protein destabilization sequences have a complementing effect.

Hence the rejection is maintained.

None of the claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong Pak whose telephone number is 571-272-0935.

The examiner can normally be reached 6:30 A.M. to 5:00 P.M. Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

/Yong D Pak/
Primary Examiner, Art Unit 1652